Narrowing in on species-specific antibiotics

Discovery

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Clostridium difficile bacteria (green) can cause life-threatening diarrheal infections and could be among the first targets of a new wave of antibiotics. Image by Med. Mic. Sciences Cardiff Uni, Wellcome Images

Is it time for drug developers to pursue new types of antibiotics? Microbiologist Jenn Leeds thinks so. A new approach is urgently needed—both to combat the problem of multi-drug resistance to current drugs and to preserve helpful bacteria in the microbiome. But it won’t be easy.
Growing up in northern New Jersey, Leeds was first captivated by microbes watching her mother culture bacteria in the laboratory of a community urologist’s office where she worked. Leeds gained an appreciation of how small, seemingly harmless organisms could wreak havoc on human health.

According to microbiologist Jenn Leeds, there are challenges to developing species-specific antibiotics.

“These are single-celled organisms with no arms and legs, no heart, and yet they have an enormous impact on all living organisms’ health and well-being,” says Leeds, Executive Director, Antibacterial Discovery for the Novartis Institutes for BioMedical Research in Emeryville, California. Her group focuses on both traditional broader-spectrum antibiotic drugs, which attack all or most types of bacteria, and newer, more-targeted approaches to antibiotic therapy.

She spoke with me about the challenges for drug developers when pursuing a new approach to antibiotic therapy, sometimes called very-narrow-spectrum or species-specific antibiotics, where the goal is to target only the microbe or microbes that are actually causing an infection. Some scientists hypothesize that targeted antibiotics could help mitigate the problem of multi-drug resistance—microbes evolving ways to skirt drugs’ killing mechanisms—which has arisen with our current use of broad-spectrum antibiotics.

This new type of antibiotic might also limit the collateral damage done to the ‘good guy’ microbes that co-exist within us performing critical functions, such as digestion. But, as Leeds also shares, several difficult scientific and clinical hurdles to developing targeted antibiotics must be overcome first.

**Would antibiotics that kill only one or two species of bacteria solve the drug resistance problem?**
Having an antibiotic that targets a specific protein or process in one species of bacteria doesn't make the issue of resistance go away. Because, even with a very-narrow-spectrum antibiotic, you will still have a selection pressure that can drive the bacteria to evolve new ways around the drug. But you are at least narrowing this selection to only the organisms you are targeting—a much smaller subset of the microbial world.

Current antibiotic drugs affect nearly every type of bacteria residing in the body, which means that dozens of susceptible species are undergoing selection by those drugs. When evolution does provide members of a species with a viable resistance mechanism, it can sometimes be transferred to other species in the community. In this way, resistance spreads faster and between many more types of bacteria, which eventually creates a higher probability of more difficult-to-treat infections.

On the other hand, a very-narrow-spectrum antibiotic that would select for resistance in only one species may greatly slow the prevalence of that new mechanism of drug-resistance showing up in other microbes.

**Would very-narrow-spectrum antibiotics limit collateral damage to the microbiome?**

There’s also a perception that these new types of antibiotics would reduce the collateral damage. In theory, such drugs would spare the beneficial microbes in our gut, for example, and reduce antibiotic-associated diarrhea, a very difficult-to-treat consequence of antibiotic therapy. That is the theory, but it remains to be tested.

But if true, then these drugs would allow doctors to treat a more targeted patient population with less use of inappropriate therapies, letting them deliver the right drug to the right patients.

**But that’s assuming that doctors know exactly which microbe is causing a patient’s distress, right?**

Right. The difficulty is that the timeline for making a treatment decision is very, very short for many types of infections. Even if you have very rapid and sensitive decision-making diagnostics, a doctor still might miss something else, another microbe that is actually the pathogen causing the disease. And many infections are poly-microbial, so a narrow-spectrum agent will have to be combined with other agents anyway in order to effectively treat the infection.

You have to know that you are not missing something—a pretty tall order for a diagnostic test. And not only do you have to rapidly find out whether a disease-causing organism is present, but you need to know if it is still susceptible to your drug. Those are the challenges that have yet to be overcome with rapid diagnostics in the clinic.

Narrow-spectrum drugs are first going to have to be used in a way that is compatible with available diagnostics. There are a few indications where the spectrum of organisms causing the problem is already typically narrow, such as lung infections in cystic fibrosis patients, some types of urinary tract infections, and gastrointestinal infections caused by Clostridium difficile.

**What are NIBR’s plans for developing very-narrow-spectrum antibiotics?**
Well, one example is, in cystic fibrosis exacerbations, the culprit is usually a form of Pseudomonas bacteria. So that is a potential narrower-spectrum path for us to pursue.

Some companies have chosen to target highly specific surface markers on a microbe rather than an internal metabolic pathway, which is likely to be shared by other microbes. Whether this provides adequate coverage of many different strains, and provides a real benefit on top of, or instead of, broader spectrum approaches remains to be demonstrated clinically.

To help develop the next generation of drugs, we also have to think about, what does a clinical diagnosis have to look like for these narrow-spectrum drugs to be used effectively? What symptoms does a particular patient population typically present with and what organisms are usually present?

So, for our narrow-spectrum projects, as with all projects, we are starting with the patient’s needs and working backwards.

**Can pharmaceutical companies abandon the development of broader-spectrum antibiotics?**

No—if a patient comes to the emergency room with symptoms of sepsis or pneumonia and needs to be treated immediately, a broader-spectrum antibiotic is often the best choice because it provides coverage in advance of any confirmation about species and drug susceptibility. Delaying treatment by even a few hours to make a bacterial species diagnosis in these patients would increase the chances of death. In these cases, broader-spectrum drugs will typically be the first line of defense, and we need to continue to discover new ones to stay a step ahead of the bacteria as they evolve resistance.

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